IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Roger R. C. New

Serial No.: 10/553,169

Filed: April 15, 2004

For: UPTAKE OF MACROMOLECULES

DECLARATION

I, Roger R. C. New, do hereby declare and state as follows:

1. I am the inventor for US Serial No. 10/553,169 (hereafter '169). I am familiar with its subject matter and am also familiar with the claims currently pending in the application.

2. I have read the Office Action that issued on application '169 with a mail date of 27 October 2009. I understand that the US Examiner has rejected the claims of application '169 on the basis that the invention as claimed would have been obvious to a person of ordinary skill in the art, in view of US 5,853,748 (hereafter '748), US 5,206,219 (hereafter '219) and a paper by Sonnenberg *et al.* I have been asked to read these three prior art documents, and comment on the differences between (i) these prior art documents, and (ii) the subject matter claimed in application '169.

3. I believe that the most important difference is that the claims of application '169 require the presence of a composition, at least 1 % by weight of which is either propyl gallate (PG), butylated hydroxy anisole (BHA), or a derivative or analogue of PG or BHA. The significance of this difference is explained below.

4. The prior art document '748 is concerned with the problem of increasing the bioavailability of active molecules - such as proteins and peptides - that are administered orally. This is explained in its opening paragraph. It is acknowledged in the paragraph bridging columns 1 and 2 of '748 that bile salts were already known to increase bioavailability. The key teaching of '748 is that the bile salts can be made more effective by combining them with an additive such as carbonate or, preferably, bicarbonate. As explained at e.g. column 6 lines 4-14 of '748, the effect of the bicarbonate is to increase the solubility of the bile salt in aqueous media. This renders the bile salts more able to exert their permeability-enhancing effect on the

epithelial cells in the intestines, thereby increasing the rate at which active molecules are absorbed.

5. In other words, '748 teaches that the already-known ability of bile salts to enhance absorption can be improved by providing an aqueous solution containing bile salts together with bicarbonate, in the intestines.

6. I understand that the Examiner has suggested that it would have been obvious to a person of ordinary skill in the art to add PG or BHA to a composition of the type described in '748, in order to help preserve it, prevent degradation, and thus increase its shelf life. I also understand that the US Patent Office Examiner has suggested that the prior art document '219 would have taught the person of ordinary skill in the art to take this step. I respectfully believe that the Examiner is wrong in these respects.

7. In particular, I do not believe that '219 would have even been of interest to a person of ordinary skill in the art seeking to preserve the bicarbonate composition of '748. That is because I understand '219 to be unconcerned with such compositions, let alone their preservation. Rather, 219 is all about a fundamentally different approach to improving bioavailability. In particular, '219 teaches to use a liquid formulation comprising:

"*a liquid polyol solvent – lipid cosolvent medium*" (see e.g. column 1 line 62)

Dissolved in this medium are:
- a proteinaceous medicament;
- an agent which facilitates the formation of a microemulsion; and
- agents to stabilize and solubilize the formulation.

8. From reading '219 I understand that the point of using such a medium, is that when such a formulation is released into the intestines it forms a microemulsion containing fatty globules. This is explained e.g. in the paragraph bridging columns 2 and 3 and at column 5 lines 48-53 of '219.

9. To summarise, I believe there is a crucial difference between the teaching of '748 and '219, namely that '748 is concerned with providing an aqueous solution of bile salt plus bicarbonate in the intestines, whereas '219 teaches to provide a microemulsion with fatty globules. On this basis, I do not believe that a person of ordinary skill in the art seeking to help preserve a bicarbonate-containing composition of '748 would have sought the answer in '219.

10. Instead, I believe that if a person of ordinary skill in the art wanted to add a preservative to one of the bicarbonate-containing compositions of '748, they would have first given thought to which known preservative(s) might be suitable. To this end, they would have been anxious to avoid prejudicing the successful formation of the important aqueous solution (of bile salt plus bicarbonate) in the intestines, because that would defeat the whole point of the

'748 compositions. For instance, the section at column 6 lines 29-46 of '748 explains that it is particularly undesirable for calcium ions to be present, because they encourage precipitation of the bile salt.

11. Accordingly, I believe that a person of ordinary skill in the art would have been anxious to avoid adding any preservative(s) that contained calcium ions or indeed any other component likely to disturb or prejudice the formation of an aqueous solution in the intestines. Therefore, in addition to ruling out calcium-containing preservatives, I believe that a person of ordinary skill in the art would have realised that to avoid disturbing the important aqueous solution formed by the '748 compositions, the only preservatives with a chance of being viable would be ones that are readily soluble in water. On this basis, I believe that (s)he would probably have contemplated adding something like vitamin C, sodium metabisulphite or malic acid, all of which are well-known preservatives that are both water soluble and GRAS-listed.

12. I certainly do not believe that a person of ordinary skill in the art would have contemplated adding PG or BHA to a '748 composition. PG and BHA both have very poor solubility in water and so are typically used only in oils or fats, i.e. non-aqueous environments. This fact is illustrated, for example, by the extracts for PG and BHA in the Handbook of Pharmaceutical Excipients by Wade and Weller, second edition.

13. Accordingly, I believe that a person of ordinary skill in the art would have assumed that adding PG or BHA would prevent the '748 composition from forming the crucial aqueous solution in the intestines. Indeed, on 2 April 2009 I signed a Declaration in connection with this case (a copy of which has, I understand, been lodged at the USPTO already), which verifies that this assumption would have been correct. That earlier Declaration confirms that if PG or BHA is added to a solution of bile acid (chenodeoxycholate) and bicarbonate, this leads to a turbid dispersion, even after incubation at 60 °C.

14. For the reasons set out above, and with all due respect to the US Patent Office Examiner, I believe that it is simply not credible to suggest that a person of ordinary skill in the art seeking to help preserve a composition of '748 would have thought to add PG or BHA to it.

15. Notwithstanding the above comments, I have been asked to consider the situation where a person of ordinary skill in the art seeking to help preserve a '748 composition had nevertheless taken it upon him or herself to consult '219. I believe that in that situation, the person of ordinary skill in the art would still not have been led to add PG or BHA. That is because, rather than displacing the above-mentioned assumption that PG or BHA would prevent the '748 composition from forming the crucial aqueous solution, the '219 document actually reinforces it. Thus, the paragraph from lines 6 to 28 of '219 confirms that PG and BHA should only be used in fatty/oily environments – they are mentioned specifically in connection with the lipid component of the '219 compositions. The only preservatives from '219 that a person of ordinary skill in the art might have contemplated adding to a '748 composition, are the hydrophilic ones mentioned at lines 25 and 26 of column 5.

16. Finally, I understand that the US Patent Office Examiner has only discussed the Sonnenberg document in connection with certain dependent claims of the '169 application, and so this document is not relevant to the points discussed above.

17. I acknowledge that wilful false statements and the like are punishable by fine or imprisonment, or both, and may jeopardize the validity of the application or any patent issuing thereon. All statements made of my own knowledge are true and all statements made on information and belief are believed to be true.

Signed

This 6 Day of January 2010.

Handbook of PHARMACEUTICAL EXCIPIENTS

Second Edition

Edited by
Ainley Wade and **Paul J Weller**

American Pharmaceutical Association
Washington

The Pharmaceutical Press
London

1994

Propyl Gallate

1. Nonproprietary Names

BP: Propyl gallate
USPNF: Propyl gallate

2. Synonyms

E310; gallic acid propyl ester; *Progallin P*; *n*-propyl gallate; propyl 3,4,5-trihydroxybenzoate; *Tenox PG*.

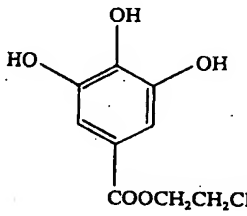
3. Chemical Name and CAS Registry Number

3,4,5-Trihydroxybenzoic acid propyl ester
[121-79-9]

4. Empirical Formula and Molecular Weight

$C_{10}H_{12}O_5$ 212.20

5. Structural Formula



6. Functional Category

Antioxidant.

7. Applications in Pharmaceutical Formulation or Technology

Propyl gallate has become widely used as an antioxidant in cosmetics, perfumes, foods and pharmaceuticals since its use in preventing autoxidation of oils was first described in 1943.[1,2] It is primarily used, in concentrations up to 0.1% w/v, to prevent the rancidity of oils and fats; it may also be used at concentrations of 0.002% w/v to prevent peroxide formation in ether and at 0.01% w/v to prevent the oxidation of paraldehyde. Synergistic effects with other antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene have been reported. Propyl gallate is also said to possess some antimicrobial properties, *see* Section 10.
Other alkyl gallates are also used as antioxidants and have approximately equivalent antioxidant properties when used in equimolar concentration; solubilities however vary, *see* Section 18.

8. Description

Propyl gallate is a white, odorless or almost odorless crystalline powder, with a bitter astringent taste which is not normally noticeable at the concentrations employed as an antioxidant.

9. Pharmacopeial Specifications

Test	BP 1993	USPNF XVII
Identification	+	+
Melting range	148-151°C	146-150°C
Loss on drying	⩽ 1.0%	⩽ 0.5%
Residue on ignition	—	⩽ 0.1%
Sulfated ash	⩽ 0.1%	—
Chloride	⩽ 330 ppm	—
Sulfate	⩽ 0.12%	—
Heavy metals	—	⩽ 0.001%
Assay (dried basis)	—	98.0-102.0%

10. Typical Properties

Antimicrobial activity: propyl gallate has been reported to possess some antimicrobial activity against Gram-negative, Gram-positive and fungal species.[3] Its effectiveness as a preservative may be improved when used in combination with zinc salts, such as zinc sulfate, due to synergistic effects.[4] Reported minimum inhibitory concentrations (MICs) for aqueous solutions containing 4% v/v ethanol as cosolvent are shown below:[3]

Microorganism	MIC (μg/mL)
Candida albicans	1500
Escherichia coli	330
Staphylococcus aureus	600

Melting point: 150°C
Solubility:

Solvent	Solubility at 20°C Unless otherwise stated
Almond oil	1 in 44
Castor oil	1 in 4.5
Cottonseed oil	1 in 81 at 30°C
Ethanol (95%)	1 in 3
	1 in 0.98 at 25°C
Ether	1 in 3
	1 in 1.2 at 25°C
Lanolin	1 in 16.7 at 25°C
Lard	1 in 88 at 45°C
Mineral oil	1 in 200
Peanut oil	1 in 2000
Propylene glycol	1 in 2.5 at 25°C
Soybean oil	1 in 100 at 25°C
Water	1 in 1000
	1 in 286 at 25°C

11. Stability and Storage Conditions

Propyl gallate is unstable at high temperatures and is rapidly destroyed in oils that are used for frying purposes.
The bulk material should be stored in a well-closed, nonmetallic container, protected from light, in a cool, dry, place.

12. Incompatibilities

The alkyl gallates, are incompatible with metals, e.g. sodium, potassium and iron, forming intensely colored complexes. Complex formation may be prevented, under some circumstances, by the addition of a sequestering agent, typically citric acid. Propyl gallate may also react with oxidizing materials.

13. Method of Manufacture

Propyl gallate is prepared by the esterification of 3,4,5-trihydroxybenzoic acid (gallic acid) with *n*-propanol. Other alkyl gallates are similarly prepared using an appropriate alcohol of the desired alkyl chain length.

14. Safety

It has been reported, following animal studies, that propyl gallate has a strong contact sensitization potential.[5] However, despite this, there have been few reports of adverse reactions.[6] Those that have been described include: contact dermatitis; [illegible]gic contact dermatitis;[7] and methemoglobinemia in neonates.[8]

The WHO has set an estimated acceptable daily intake for propyl gallate at up to 2.5 mg/kg body-weight.[9]

LD_{50} (cat, oral): 0.4 g/kg[10]
LD_{50} (mouse, oral): 1.7 g/kg
LD_{50} (rat, oral): 3.8 g/kg
LD_{50} (rat, IP): 0.38 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. When heated to decomposition propyl gallate may emit toxic fumes and smoke.

16. Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM injections and topical preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

[illegible], Br, Cz, Egypt, Fr, Ind, Nord and USPNF.

18. Related Substances

Dodecyl gallate; ethyl gallate; octyl gallate.

Dodecyl gallate: $C_{19}H_{30}O_5$
Molecular weight: 338.44
CAS number: [1166-52-5]
Synonyms: dodecyl 3,4,5-trihydroxybenzoate; E312; lauryl gallate.
Pharmacopeias: Aust, Br and Fr.
Appearance: white, odorless or almost odorless crystalline powder.
Melting point: 96-97.5°C
Solubility:

Solvent	Solubility at 20°C
Acetone	1 in 2
Chloroform	1 in 60
Ethanol (95%)	1 in 3.5
Ether	1 in 4
Methanol	1 in 1.5
Peanut oil	1 in 30
Propylene glycol	1 in 60
Water	practically insoluble

Ethyl gallate: $C_9H_{10}O_5$
Molecular weight: 198.17
CAS number: [831-61-8]
Synonyms: ethyl 3,4,5-trihydroxybenzoate.
Pharmacopeias: Br.
Appearance: white, odorless or almost odorless, crystalline powder.
Melting point: 151-154°C
Solubility:

Solvent	Solubility at 20°C
Ethanol (95%)	1 in 3
Ether	1 in 3
Peanut oil	practically insoluble
Water	slightly soluble

Octyl gallate: $C_{15}H_{22}O_5$
Molecular weight: 282.34
CAS number: [1034-01-1]
Synonyms: E311; octyl 3,4,5-trihydroxybenzoate.
Pharmacopeias: Br and Fr.
Appearance: white, odorless or almost odorless crystalline powder.
Melting point: 100-102°C
Solubility:

Solvent	Solubility at 20°C
Acetone	1 in 1
Chloroform	1 in 30
Ethanol (95%)	1 in 2.5
Ether	1 in 3
Methanol	1 in 0.7
Peanut oil	1 in 33
Propylene glycol	1 in 7
Water	practically insoluble

19. Comments

Propyl gallate has been reported to impart an 'off' flavor to corn and cottonseed oils when used as an antioxidant.[11]

An acceptable daily intake for dodecyl gallate and octyl gallate was not set by the WHO due to insufficient data. The use of octyl gallate in beer and other widely consumed beverages was however not recommended by the WHO due to the possibility of adverse reactions in the buccal mucosa of individuals previously sensitized by cutaneous contact with this compound.[9]

20. Specific References

1. Boehm E, Williams R. The action of propyl gallate on the autoxidation of oils. Pharm J 1943; 151: 53.
2. Boehm E, Williams R. A study of the inhibiting actions of propyl gallate (normal propyl trihydroxy benzoate) and certain other trihydric phenols on the autoxidation of animal and vegetable oils. Chemist Drugg 1943; 140: 146-147.
3. Zeelie JJ, McCarthy TJ. The potential antimicrobial properties of antioxidants in pharmaceutical systems. S Afr Pharm J 1982; 49: 552-554.
4. McCarthy TJ, Zeelie JJ, Krause DJ. The antimicrobial action of zinc ion/antioxidant combinations. J Clin Pharm Ther 1992; 17: 51-54.

5. Kahn G, Phanuphak P, Claman HN. Propyl gallate contact sensitization and orally induced tolerance. Arch Dermatol 1979, 104: 506-509.
6. Golightly LK, Smolinske SS, Bennett ML, Sutherland EW, Rumack BH. Pharmaceutical excipients: adverse effects associated with 'inactive' ingredients in drug products (part II). Med Toxicol 1988; 3: 209-240.
7. Bojs G, Nicklasson B, Svensson A. Allergic contact dermatitis to propyl gallate. Contact Dermatitis 1987; 17: 294-298.
8. Nitzan M, Volovitz B, Topper E. Infantile methemoglobinemia caused by food additives. Clin Toxicol 1979; 15(3): 273-280.
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10. Sweet DV, editor. Registry of toxic effects of chemical substances. Cincinnati: US Department of Health, 1987.
11. McConnell JEW, Esselen WB. Effect of storage conditions and antioxidants on the keeping quality of packaged oils. J Am Oil Chem Soc 1947; 24: 6-14.

21. General References

Johnson DM, Gu LC. Autoxidation and antioxidants. In: Swarbrick J, Boylan JC, editors. Encyclopedia of pharmaceutical technology, volume 1. New York: Marcel Dekker Inc, 1988: 415-449.

22. Authors

UK: PJ Weller.

Butylated Hydroxyanisole

1. Nonproprietary Names

BP: Butylated hydroxyanisole
USPNF: Butylated hydroxyanisole

2. Synonyms

Antrancine 12; BHA; *tert*-butyl-4-methoxyphenol; 1,1-dimethylethyl-4-methoxyphenol; E320; *Embanox BHA*; *Nipanox BHA*; *Nipantiox 1-F*; *PM 1787*; *PM 1788*; *PM 12366*; *Sustane 1-F*; *Tenox BHA*.

3. Chemical Name and CAS Registry Number

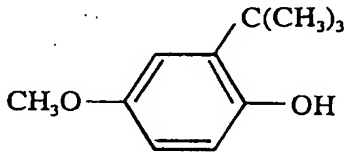
2-*tert*-Butyl-4-methoxyphenol [25013-16-5]

4. Empirical Formula Molecular Weight

$C_{11}H_{16}O_2$ 180.25

The BP 1993 describes butylated hydroxyanisole as 2-*tert*-butyl-4-methoxyphenol containing a variable amount of 3-*tert*-butyl-4-methoxyphenol.

5. Structural Formula



6. Functional Category

Antioxidant.

7. Applications in Pharmaceutical Formulation or Technology

Butylated hydroxyanisole is an antioxidant with some antimicrobial properties.[1] It is used in cosmetics, foods and pharmaceuticals particularly to delay or prevent oxidative rancidity of fats and oils and to prevent loss of activity of oil-soluble vitamins.

Butylated hydroxyanisole is frequently used in combination with other antioxidants, particularly butylated hydroxytoluene and alkyl gallates, and with sequestrants or synergists such as citric acid.

Antioxidant use	Concentration (%)
β-Carotene	0.01
Essential oils and flavoring agents	0.02-0.5
IM injections	0.03
IV injections	0.0002-0.0005
Oils and fats	0.02
Topical formulations	0.005-0.02
Vitamin A	10 mg per million units

8. Description

Butylated hydroxyanisole occurs as a white or almost white crystalline powder or a yellowish-white waxy solid with a faint, characteristic aromatic odor.

9. Pharmacopeial Specifications

Test	BP 1993 (Ad 1994)	USPNF XVII (Suppl 6)
Identification	+	+
Residue on ignition	—	⩽ 0.01%
Sulfated ash	⩽ 0.05%	—
Related substances	+	—
Arsenic	—	⩽ 3 ppm
Heavy metals	—	⩽ 0.001%
Organic volatile matter	—	+
Assay	—	⩾ 98.5%

10. Typical Properties

Antimicrobial activity: activity is similar to that of the *p*-hydroxybenzoate esters (parabens). The greatest activity is against molds and Gram-positive bacteria, with less activity against Gram-negative bacteria.

Boiling point: 264°C

Melting point: 47°C (for pure 2-*tert*-butyl-4-methoxyphenol), *see also* Section 19.

Solubility: practically insoluble in water; freely soluble in ⩾ 50% aqueous ethanol, propylene glycol, chloroform, ether, hexane, cottonseed oil, peanut oil, soybean oil and in solutions of alkali hydroxides. *See also* HPE Data.

Specific gravity: 1.05 at 20°C

Viscosity (kinematic): 3.3 mm^2/s (3.3 cSt) at 99°C

	HPE Laboratory Project Data		
	Method	Lab #	Results
Density	DE-1	31	1.117 g/cm^3
Solubility			
Ethanol (95%) at 25°C	SOL-7	32	793.0 mg/mL
Ethanol (95%) at 37°C	SOL-7	32	834.0 mg/mL
Hexane at 25°C	SOL-7	32	48.0 mg/mL
Hexane at 37°C	SOL-7	32	10.0 mg/mL
Propylene glycol at 25°C	SOL-7	32	467.0 mg/mL
Propylene glycol at 37°C	SOL-7	32	456.0 mg/mL
Water at 25°C	SOL-7	32	0.32 mg/mL
Water at 37°C	SOL-7	32	0.78 mg/mL

Supplier: Eastman Fine Chemicals.

11. Stability and Storage Conditions

Exposure to light causes discoloration and loss of activity. Butylated hydroxyanisole should be stored in a well-closed container, protected from light, in a cool, dry, place.

12. Incompatibilities

Butylated hydroxyanisole is phenolic and undergoes reactions characteristic of phenols. It is incompatible with oxidizing agents and ferric salts. Trace quantities of metals, and exposure to light, cause discoloration and loss of activity.

13. Method of Manufacture

Prepared by the reaction of *p*-methoxyphenol with isobutene.

14. Safety

Butylated hydroxyanisole is absorbed from the gastrointestinal tract and is metabolized and excreted in the urine with less than 1% unchanged within 24 hours of ingestion.[2] Although there have been some isolated reports of adverse skin reactions to butylated hydroxyanisole[3,4] it is generally regarded as nonirritant and nonsensitizing at the levels employed as an antioxidant.

Concern over the use of butylated hydroxyanisole has occurred following long-term animal feeding studies. Although previous studies in rats and mice fed butylated hydroxyanisole at several hundred times the US permitted level in the human diet showed no adverse effects, a study in which rats, hamsters and mice were fed butylated hydroxyanisole at 1-2% of the diet produced benign and malignant tumors of the forestomach, but in no other sites. However, humans do not have any region of the stomach comparable to the rodent forestomach and studies in animals that also do not have a comparable organ (dogs, monkeys and guinea pigs) showed no adverse effects. Thus, the weight of evidence does not support any relevance to the human diet where butylated hydroxyanisole is ingested at much lower levels.[5] The WHO acceptable daily intake of butylated hydroxyanisole has been set at 500 μg/kg body-weight.[5]

LD_{50} (mouse, oral): 2.0 g/kg[6]
LD_{50} (rat, IP): 0.88 g/kg
LD_{50} (rat, oral): 2.2 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Butylated hydroxyanisole may be irritant to the eyes, skin, and on inhalation. It should be handled in a well-ventilated environment; gloves and eye protection are recommended.

16. Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations, IM and IV injections, oral capsules and tablets, rectal, topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Br, Fr, Ind, It, Mex and USPNF.

18. Related Substances

Butylated Hydroxytoluene.

19. Comments

The commercially available material can have a wide melting point range (47-57°C) due to the presence of varying amounts of 3-*tert*-butyl-4-methoxyphenol.

Tenox brands contain 0.1% w/w citric acid as a stabilizer.

20. Specific References

1. Lamikanra A, Ogunbayo TA. A study of the antibacterial activity of butyl hydroxy anisole (BHA). Cosmet Toilet 1985; 100(10): 69-74.
2. El-Rashidy R, Niazi S. A new metabolite of butylated hydroxyanisole in man. Biopharm Drug Dispos 1983; 4: 389-396.
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5. FAO/WHO. Evaluation of certain food additives and contaminants. Thirty-third report of the joint FAO/WHO expert committee on food additives. Tech Rep Ser Wld Hlth Org 1989; No. 776.
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21. General References

Babich H, Borenfreund E. Cytotoxic effects of food additives and pharmaceuticals on cells in culture as determined with the neutral red assay. J Pharm Sci 1990; 79: 592-594.
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22. Authors

USA: MJ Groves.